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REACTIVITY OF C-NUCLEOPHILIC COMPOUNDS WITH PARTICULAR
CONSIDERATION OF PYRYLIUM AND THIOPYRYLIUM SALTS, 1ST REPORT

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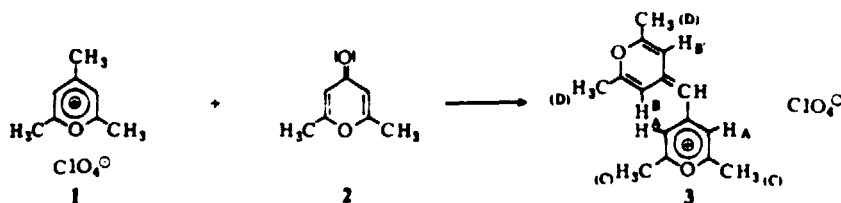
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16. Abstract The reactivity of C-nucleophilic pyrylium and thio-pyrylium salts towards derivatives of γ -pyrone was studied. The new compounds 3, 5-12, 15, 17, 20a-20f, 21 and 22 were obtained.			
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REACTIVITY OF C-NUCLEOPHILIC COMPOUNDS WITH PARTICULAR CONSIDERATION OF PYRYLIUM AND THIOPYRYLIUM SALTS, 1ST REPORT

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In the framework of our investigations of organic cations we/236* were interested in the reactivity of pyrylium, thiopyrylium and selenopyrylium salts as C-nucleophiles toward corresponding carbonyl-active reactants. The first report on condensation of methylpyrylium salts with aromatic aldehydes was published by Dilthey and Fischer¹, and Wizinger et al.² also investigated the reactivity of substituted pyrylium salts.

Thus, the objective was to, on the one hand, investigate the reactivity of trimethyl-substituted pyrylium salts toward γ -pyrones and γ -thiopyrones and, on the other hand, test the reactivity of methylpyrylium, methylthiopyrylium and methylselenopyrylium salts toward aromatic aldehydes, flavones and thioflavones.

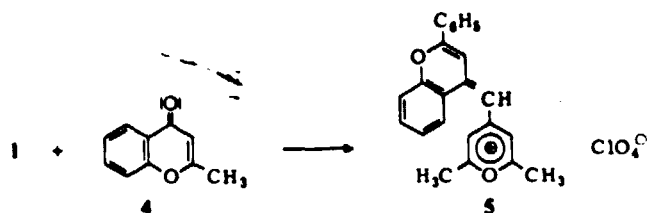


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The 2,4,6-trimethylpyrylium perchlorate (1) condensed with 2,6-dimethyl- γ -pyrone (2) on the γ -stable CH_3 group into 3; di- or tri-condensation products could not be detected even with the use of stronger reaction conditions. The ^1H -NMR spectrum of 3 -- in CF_3COOH -- showed at room temperature a singlet in the aliphatic range at $\delta = 2.85$ ppm of rel. intensity 12 for the 4 CH_3 groups; in the olefinic range appeared a singlet at $\delta = 4.58$ ppm of rel. int. 1 for the methine group and in the aromatic range a singlet at $\delta = 7.85$ ppm of rel. int. 4 for the β -stable protons.

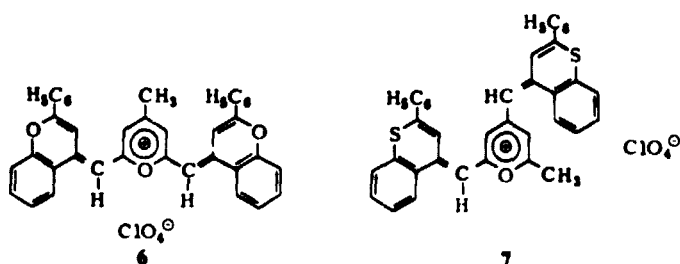
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From the magnetic identity H_A and H_B , and $H_{A'}$; $H_{B'}$, as well as of $(CH_3)_C$, $(CH_3)_D$ or $(CH_3)_C$, $(CH_3)_D$, a rotation of both pyrylium rings around their bonds to the methine group can be assumed.

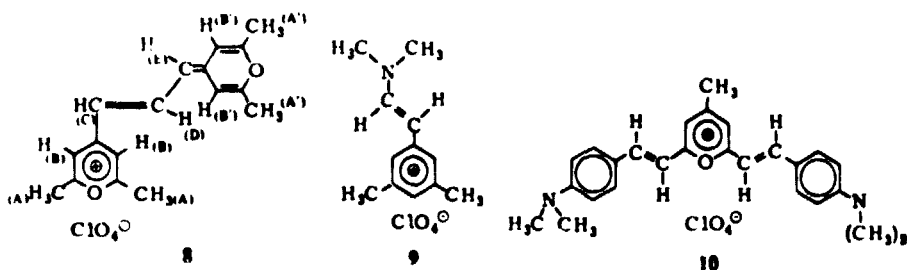


Condensation of 1 with the flavone 4, even with the use of excessive amounts of 4, produced isolation of only 5; the 1H -NMR spectrum of 5 -- in CF_3COOH at 60 degrees -- showed a singlet at $\delta = 2.88$ ppm (rel. int. 6), a singlet at $\delta = 5.07$ ppm (rel. int. 1) and a multiplet at $\delta = 7.6-8.4$ ppm (rel. int. 12).

On the other hand, if 1 and 4 are made to react in the melt at higher temperatures (approximately 190 degrees) the yield, aside from a little of 5, is primarily 6; under corresponding reaction conditions compound 7 was isolated with thioflavone.

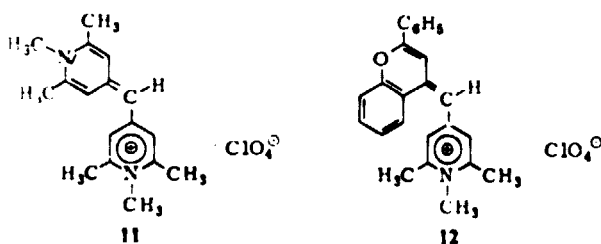


Additional investigations involved reactivity of 1 towards /238 orthoformic acid ethylester, N,N-dimethyl formamide and p-dimethyl aminobenzaldehyde, which yielded cyanin dyes 8, 9, 10.

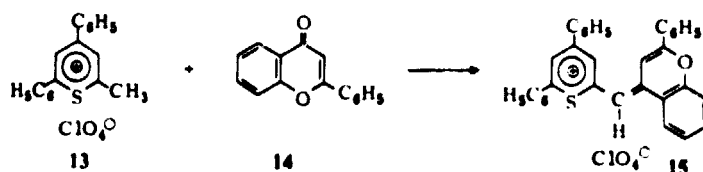


A reaction in a ratio of 1:1 occurred in the case of compound 8 on the γ -stable CH_3 group of 1; $^1\text{H-NMR}$ spectroscopic studies in CF_3COOH at 60 degrees showed one singlet in the aliphatic range at $\delta = 2.88$ ppm (rel. intensity 12) for the protons A and A', and for aromatic protons B as well as B' a singlet at $\delta = 8.8$ ppm (relative intensity 4). Reaction on the γ - CH_3 group of 1 occurred also with N,N-dimethyl formamide; in its $^1\text{H-NMR}$ spectrum -- measured in CD_3CN at 60 degrees -- there was a sharp singlet in the aliphatic range at $\delta = 2.25$ ppm (rel. intensity 6) for the CH groups of the pyrylium nucleus, at $\delta = 3.05$ ppm as well as 3.30 ppm there were 2 singlets of the dimethylamino group (rel. intensity 6). Both protons of the methine grouping formed 2 doublets at $\delta = 5.75$ and 7.98 ppm with $J = 12$ Hz for transcoupling of both protons; the aromatic protons of the pyrylium nucleus occurred as singlets at $\delta = 6.85$ ppm. On the other hand, p-dimethyl aminobenzaldehyde reacted, as already mentioned, with both CH_3 groups bonded in the 2.6 position of 1 and yielding 10.

It was possible to convert the pyrylium salts 3 and 5 into the pyridinium salts 11 and 12.

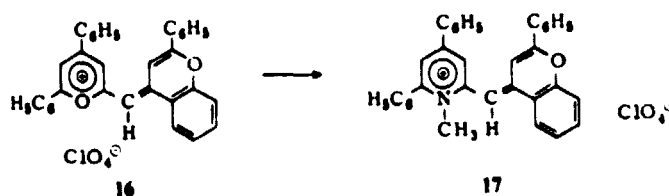


The acetanhydride method made it possible to obtain from 2-methyl-4,6-diphenyl pyryliumperchlorate and from its thio-analog with flavones and chromones as carbonyl-active reagents a number of new monomethinecyanin compounds forming partly in yields of approximately 90%; these were subsequently converted through O,N-exchange into the corresponding pyridiniummonomethincyanins.

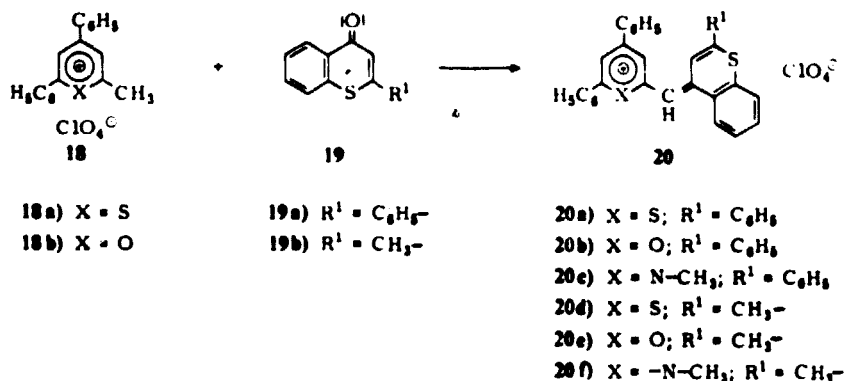


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From 2-methyl-4,6-diphenyl-thiopyryliumperchlorate (13) by means of flavone 14 was obtained salt 15, from 2-methyl-4,6-diphenylpyryliumperchlorate and 14 was obtained salt 16 which could be converted into the corresponding pyridinium salt 17 by means of N-methylamine:



18a, 18b and substituted thioflavones yielded, under cleavage of 1 mol H₂O in acetanhydride as solvent, the salts 20a, 20b as well as 20d and 20e, with methylamine it was possible to obtain without any difficulties from 20b the compound 20c, from 20e 20f.



Also the tricyclic -pyrone, namely thioxanthone, condensed with the thiopyrylium salt 18a or with the pyrylium salt 18b into the monomethinecyanins 21 and 22:

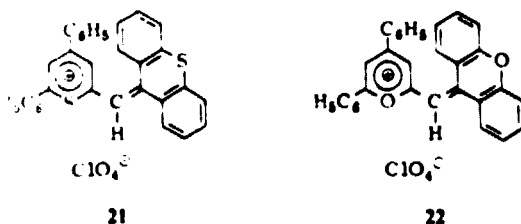


Table 1 summarizes the results of UV-spectroscopic studies.

TABLE 1: ABSORPTION MAXIMA OF THE SYNTHETIZED COMPOUNDS

Compound	λ_{max} (nm) (log ϵ)	Solvents
3	470 (4,529)	Eisessig/HClO ₄
4	523 (4,534)	Eisessig/HClO ₄
5	655 (4,223) 556 (4,435)	Eisessig/HClO ₄
6	590 (4,508)	Eisessig/HClO ₄
7	585 (4,651)	Eisessig/HClO ₄
8	402 (4,665)	Eisessig/HClO ₄
9	670 (4,673)	Ethanol
10	477 (5,170)	Acetonitrile
11	453 (4,485)	Eisessig
12	600 (4,392)	Eisessig/HClO ₄
13	450 (4,217)	Ethanol
14a	644 (3,959)	Eisessig/HClO ₄
14b	635 (4,015)	Eisessig/HClO ₄
14c	467 (4,289)	Ethanol
14d	625 (4,453)	Eisessig/HClO ₄
14e	625 (4,453)	Eisessig/HClO ₄
14f	455 (3,997)	Acetonitrile
15	554 (3,528)	Ethanol
16	568 (3,654)	Chloroform
17	551 (3,811)	Ethanol
18	576 (4,113)	Chloroform

(TN: Eisessig = glacial acetic acid)

Experimental Part

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Melting point not corrected, melting points were determined by means of the Lindström apparatus, the ¹H-NMR spectra by the instrument JMN-MH-60 Mark 2 of the Jeol company, IR spectra with the spectrometer Perkin-Elmer 257, UV spectra with the automatically registering UV spectrophotometer RPQ 20 A V of the Zeiss company, elementary analysis was carried out in the microanalytical laboratory of the company Ilse Beetz, Kronach/Oberfranken, and mass spectra with the mass-spectrometer CH-5 of the company Varian Ltd in Bremen. We thank Dr. H. Seel for having provided the ¹H-NMR spectra, prof. Dr. H. Musso, prof. Dr. G. Schröder as well as Dr. U. Zahorszky, Institute for Organic Chemistry of the University of Karlsruhe.

[Bis-4-(2,6-dimethylpyrrolo)]-monomethinecyanin-perchlorate (3)

1.1 g (5 mmol) of 2,4,6-trimethylpyryliumperchlorate (1) and 1.86 g (15 mmol) of 2,6-dimethylpyrone-4 (2) are mixed in 30 ml acetanhydride and heated while mixing for 3 h to 100 degrees. Red needles,

melting point 198-200 degrees (glacial acetic acid); yield 0.78 g (48%). $C_{15}H_{17}ClO_6$ (328.75) calculated: C 54.87 H 5.22 Cl 10.79; found: C 54.98 H 5.08 Cl 10.68.

[4-(2,6-dimethylpyrrolo)]-(4-flavylo)-monomethinecyaninperchlorate (5)

0.88 g (4 mmol) of 1 and 0.88 g (4 mmol) of flavone 4 are heated in 20 ml acetanhydride for 16 h to 100 degrees, after cooling and keeping the reaction mixture under refrigeration green sparkling crystals; melting point 223-225 degrees (glacial acetic acid); yield 1.22 g (63%). C H ClO (426.9) calculated: C 64.71 H 4.48 Cl 8.30; found: C 64.79 H 4.46 Cl 7.96.

[2,6-(4-methylpyrrolo)]-[bis-4(4-flavylo)]-monomethinecyaninperchlorate (6)

1.1 g (5 mmol) of 1 and 5 g (22 mmol) of 4 are heated in oil bath for 30 min at 190 degrees, the mass is mixed with 50 ml benzol and is let to cool, the crystals scrubbed with glacial acetic acid and ether. Brownish-red crystals from glacial acetic acid. Melting point > 310 degrees; yield 0.7 g (22%). $C_{38}H_{27}ClO_7$ (631.05) calculated: C 72.32 H 4.31 Cl 5.62; found: C 72.00 H 4.34 Cl 5.44. 1H -NMR (60 MHz; CF_3COOH): δ = 2.82 ppm (s, CH_3), 5.02 (s, $CH=$), 6.75-8.7 (m, aromatic H). -

[2,4-(6-methylpyrrolo)]-[bis(4-thioflavylo)]-mono-methinecyanin-perchlorate (7)

0.88 g (4 mmol) of 1 are heated with 0.95 g (4 mmol) of thioflavone in 20 ml acetanhydride for 16 hrs to 100 degrees, let to cool, following 2-day refrigeration violet needles are extracted. Melting point > 310 degrees; yield 0.5 g (19%). $C_{38}H_{27}ClO_5S_2$ (663.22) calculated: C 68.82 H 4.10 S 5.34 Cl 9.67; found: C 68.45 H 4.18 S 5.07 Cl 9.02.

1H -NMR (60 MHz; CF_3COOH): δ = 2.64 ppm (s, CH_3-), 4.95 (s, $-CH=$), 5.25 (s, $\gamma-CH=$), 7.67-8.84 (m, aromatic H). -

[Bis-4-(2,6-dimethylpyrrolo)]-trimethinecyanin-perchlorate (8)

A solution of 1.3 g (6 mmol) of 1, 1 ml orthoformic acid ethylester and 1 ml pyridine are heated in 40 ml glacial acetic acid/acetanhydride (1:1) for 30 min to approximately 130-140 degrees (oil bath

temperature), subsequently let to cool and, after standing at room temperature for several hours, extracted, dark brown crystals from glacial acetic acid recrystallized. Melting point 290 degrees; yield 1.27 g (61%). $C_{17}H_{11}ClO_6$ (354.73) calculated: C 57.54 H 5.39 Cl 10.00; found: C 57.39 H 5.26 Cl 9.90.

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[4-(2,6-dimethylpyrrolo-)]-(N,N-dimethylformamido-)-monomethinecyanin-perchlorate (9)
0.55 g (2.5 mmol) of 1 and 3.3 g (45 mmol) of N,N-dimethylformamide are heated in 10 ml acetic anhydride for 16 hrs to 130-140 degrees (oil bath temperature), let to cool and the orange-colored crystals are carefully precipitated with ether. Melting point 210-211 degrees (acetonitrile); yield 0.65 g (94%). $C_{11}H_{16}ClNO_5$ (277.71) calculated: C 47.57 H 5.81 Cl 12.77 N 5.05; found: C 47.67 H 5.46 Cl 12.72 N 5.07.

[2,6-bis-(dimethylaminostyryl-)]-4-methyl-pyryliumperchlorate (10)
0.4 g (1.8 mmol) of 1 are heated with 5 g of N,N-dimethyl-aminobenzaldehyde in 5 ml of glacial acetic acid for 45 min to approximately 190 degrees (oil bath temperature), after cooling the red-violet crystals are precipitated with ether. Melting point 200-203 degrees (glacial acetic acid); yield 0.5 g (57%). $C_{26}H_{29}ClN_2O_5$ (484.98) calculated: C 64.38 H 6.03 N 5.78; found: C 64.19 H 6.18 N 6.13.

[Bis-4-(1,2,6-trimethylpyridino)]-monomethinecyaninperchlorate (11)
0.23 g (0.7 mmol) of 3 in 20 ml ethanol and 1 ml of a 40% aqueous solution of CH_3NH_2 are heated for 45 min in reflux, let to cool and crystallize under refrigeration; brick-red crystals from ethanol/ H_2O (5:1). Melting point 226 degrees; yield 0.21 g (54%). $C_{17}H_{23}ClN_2O_4$ (354.83) calculated: C 57.54 H 6.53 N 7.89; found C 57.55 H 6.65 N 7.42.
 1H -NMR (60 MHz, CF $_3$ COOH): δ = 2.9 ppm (s, 4CH $_3$ -), 4.23 (s, 2N-CH $_3$), 4.47 ppm (s, CH=), 7.72 (s, 4aromatic H).

[4-(1,2,6-trimethylpyridino)]-(4-flavylo)-monomethinecyaninperchlorate (12)
From 1 g (0.2 mmol) of 5 analogously to (11); yellow crystals. Melting point 153-154 degrees (ethanol); yield 0.9 g (87%). $C_{24}H_{22}ClNO_5$ (439.89) calculated: C 65.53 H 5.04 N 3.18; found: C 66.46 H 4.71 N 2.97.

[2-(4,6-diphenylthiopyrilo-)]-(4-flavylo-)-monomethinecyaninperchlorate (15)
 0.9 g (2.5 mmol) of 2-methyl-4,6-diphenylthiopyryliumperchlorate (13) are heated with 0.55 g (2.5 mmol) of flavone 14 in 20 ml of acetanhydride for 16 hrs to 100 degrees. After cooling let to crystallize under refrigeration, blue crystals. Melting point 278 degrees (acetanhydride/glacial acetic acid 3:1); yield 1.04 g (75%). $C_{33}H_{23}ClO_5S$ (567.06) calculated: C 69.89 H 4.09 Cl 6.25 S 5.66; found: C 70.14 H 4.21 Cl 6.16 S 4.33.

[2-(4,6-diphenylpyrilo-)]-(4-flavylo-)-monomethinecyaninperchlorate (16)
 From 1.73 g (5 mmol) of 13 and 1.11 g (5 mmol) of 14 analogously to (15). Green needles from acetanhydride/glacial acetic acid (3:1); melting point 247-250 degrees; yield 2.5 g (91%). $C_{33}H_{23}ClO_6$ (550.9) calculated: C 71.93 H 4.21 Cl 6.44; found: C 71.32 H 4.18 Cl 6.01.

[2-(1-methyl-4,6-diphenylpyridino-)]-(4-flavylo-)-monomethinecyaninperchlorate (17)
 From 0.5 g (1 mmol) of 16 analogously to (11), brick-red crystals. Melting point 150-153 degrees (ethanol); yield 0.4 g (78%). $C_{34}H_{26}ClNO_5$ (564.04) calculated: C 72.4 H 4.65 N 2.48; found: C 72.46 H 4.61 N 2.86.

[2-(4,6-diphenylthiopyrilo-)]-(4-thioflavylo-)-monomethinecyanin-perchlorate (20a)
 From 0.9 g (2.5 mmol) of 18a and 0.58 g (2.5 mmol) of thioflavone analogously to (15). Red-violet crystals. Melting point 256 degrees (glacial acetic acid); yield 1.4 g (97%). $C_{33}H_{23}ClO_4S_2$ (583.12) calculated: C 67.97 H 3.98 Cl 6.08; found: C 68.36 H 4.04 Cl 6.11.

[2-(4,6-diphenylpyrilo-)]-4(4-thioflavylo)-monomethinecyanin-perchlorate (20b) ^{/243}
 From 1.73 g (5 mmol) of 18b and 1.19 g (5 mmol) of thioflavone in analogy to (15). Golden-bronze shining crystals. Melting point 261 degrees (glacial acetic acid/acetanhydride); yield 2.24 g (79%). $C_{33}H_{23}ClO_4S$ (567.06) calculated: C 69.89 H 4.09 Cl 6.25 S 5.66; found: C 70.02 H 4.02 Cl 6.31 S 5.63.

[2-(1-methyl-4,6-diphenylpyridino)]-[4-thioflavylo]-monomethinecyanin-perchlorate (20c)

From 0.6 g (1 mmol) of 20b analogously to (11), red crystals.

Melting point 150 degrees (ethanol); yield 0.2 g (33%).

$C_{34}H_{26}ClNO_4S$ (580.1) calculated: C 70.39 H 4.51 N 2.42 S 5.53;

found: C 70.12 H 4.22 N 2.44 S 5.12.

[2-(4,6-diphenylthiopyrilo)]-[4-(2-methylthiochromylo)]-monomethinecyanin-perchlorate (20d)

From 0.9 g (2.5 mmol) of 18a and 0.44 g (2.5 mmol) of methylthiochromone analogously to (15); red-violet crystals, melting point 258 degrees (glacial acetic acid); yield 0.93 g (72%). $C_{28}H_{21}ClO_4S_2$ (521.06) calculated: C 64.54 H 4.06 Cl 6.81; found C 65.04 H 4.13 Cl 6.31.

[2-(4,6-diphenyl-pyrilo)]-[4-2methylthiochromylo]-monothiocyantin-perchlorate (20e)

From 1.73 g (5 mmol) of 18b and 0.88 g (5 mmol) of 2-methyl-thiochromone analogously to (15). Red-violet crystals, melting point 276 degrees (glacial acetic acid/acetanhydride 3:1); yield 1.6 g (63%). $C_{28}H_{21}ClO_5S$ (504.9) calculated: C 66.59 H 4.19 S 6.35; found: C 66.38 H 4.31 S 6.63.

[2-(1-methyl-4,6-diphenylpyridino)]-[4-(2-methylthiochromylo)]-monomethinecyanin-perchlorate (20f)

From 0.6 g (1.2 mmol) of 20e analogously to (11); brown crystals, melting point 134-185 degrees (glacial acetic acid); yield 0.4 g (67%). $C_{29}H_{24}ClNO_4S$ (518.04) calculated: C 67.24 H 4.67 S 6.19 Cl 6.89; found: C 66.36 H 4.65 S 6.62 Cl 6.73.

[2-(4,6-diphenylthiopyrilo)]-[4-thioxanthyllo]-monomethinecyanin-perchlorate (21)

From 0.9 g (2.5 mmol) of 18b and 0.52 g (2.5 mmol) of thioxanthone analogously to (15). Black crystals, melting point 218-219 degrees (ethanol); yield 0.8 g (50%). $C_{31}H_{21}ClO_4S_2$ (557.09) calculated: C 66.83 H 3.80 S 11.51; found: C 66.70 H 3.82 S 11.02.

[2-(4,6-diphenylpyrrolo)]-(9-thioxanthyl)-monomethinecyaninsulphoacetate (22)
From 1.93 g (5 mmol) 2-methyl-4,6-diphenylpyrylium-sulphoacetate
and 1.05 g (5 mmol) thioxanthone in 30 ml acetic anhydride analogously
to (15). Black-violet shining crystals; melting point 129.5
degrees (ethanol); yield 0.5 g (17%). $C_{31}H_{24}O_6S_2$ (580.68) calcu-
lated: C 68.25 H 4.17 S 11.05; found: C 67.39 H 4.16 S 11.03.

REFERENCES

1. Dilthey, W. and J. Fischer, Ber. Dtsch. Chem. Ges. 57, 1653 (1924).
2. Wizinger, R. and J. Kelemen, Helv. Chim. Acta 45, 1918 (1962).
3. Arndt, F., H. Scholz and E. Aron, Ber. Dtsch. Chem. Ges. 69, 2379 (1936).
4. King, C., J. Am. Chem. Soc. 73, 300 (1951).

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